# Proposed Decision Memo for Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers (CAG-00181N)

## Decision Summary

The Centers for Medicare and Medicaid Services (CMS) is seeking public comment on our proposed determinations related to the use of FDG PET as a diagnostic test for various forms of cancer.

CMS has proposed that there is sufficient evidence to conclude that an FDG PET scan for the detection of pre-treatment metastases in newly diagnosed cervical cancer subsequent to negative conventional imaging would be reasonable and necessary, and CMS proposes to issue a national coverage determination (NCD) for this indication.

CMS has proposed that the evidence is sufficient to conclude that an FDG PET scan for staging or detecting recurrent or residual disease in testicular cancer would not be reasonable and necessary, and CMS proposes to issue a national non-coverage determination for this indication.

For all other indications in this decision memorandum, CMS has proposed that the evidence is sufficient to conclude that an FDG PET scan would be reasonable and necessary only when the provider is participating in and patients are offered enrollment in one of the following three types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (IDE); or
- A clinical trial consistent with the evidentiary requirements for National Coverage Analyses (See Appendix A) and meeting specific quality standards (see Appendix B);or
- An FDG PET registry that is designed to provide additional information on the diagnostic accuracy and clinical utility of FDG PET for diagnosis, staging, restaging, and/or monitoring of one or more cancers. Qualifying registries must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are appropriately credentialed to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and hospitals and providers who do not comply with the data collection requirements are removed from the registry.

All other previous positive national coverage determinations will remain in effect. (See Appendix C.)

All other previous national non-coverage determinations based on evidence of lack of benefit will remain in effect. (See Appendix C.)

For all other indications for which CMS currently has a noncoverage determination (see Appendix C), CMS has proposed that an FDG PET scan would be reasonable and necessary only when the provider is participating in and patients are offered enrollment in one of the three types of prospective clinical studies described above.

We are requesting public comment on these proposed determinations pursuant to Section 731 of the Medicare Modernization Act.

Back to Top

# Proposed Decision Memo

TO: Administrative File: CAG 00181N Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers

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SUBJECT: Proposed Decision: Positron Emission Tomography (FDG) for Brain, Cervical, Ovarian, Pancreatic, Small Cell Lung, and Testicular Cancers

DATE: November 1, 2004

**I. Proposed Decision**

The Centers for Medicare and Medicaid Services (CMS) is seeking public comment on our proposed determinations related to the use of FDG PET as a diagnostic test for various forms of cancer.

CMS has proposed that there is sufficient evidence to conclude that an FDG PET scan for the detection of pre-treatment metastases in newly diagnosed cervical cancer subsequent to negative conventional imaging would be reasonable and necessary, and CMS proposes to issue a national coverage determination (NCD) for this indication.

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- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (IDE); or
- A clinical trial consistent with the evidentiary requirements for National Coverage Analyses (See Appendix A) and meeting specific quality standards (see Appendix B);or
- An FDG PET registry that is designed to provide additional information on the diagnostic accuracy and clinical utility of FDG PET for diagnosis, staging, restaging, and/or monitoring of one or more cancers. Qualifying registries must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are appropriately credentialed to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and hospitals and providers who do not comply with the data collection requirements are removed from the registry.

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We are requesting public comment on these proposed determinations pursuant to Section 731 of the Medicare Modernization Act.

**II. Background**

FDG PET is a minimally-invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseases such as cancer, ischemic heart disease, and some neurological disorders. 2-[F-18] Fluoro-D-Glucose (FDG) is an injected radioactive tracer substance (radionuclide) that gives off sub-atomic particles, known as positrons, as it decays. FDG PET uses a positron camera (tomograph) to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on glucose metabolism of the tissue being studied. As malignancies can cause abnormalities of metabolism and blood flow, FDG PET evaluation can indicate the probable presence or absence of malignancy based upon observed differences in biologic activity of adjacent tissues.

Diagnostic imaging technologies such as x-ray films, computed tomography (CT), and magnetic resonance imaging (MRI) supply information about the anatomic structure of suspected malignancies, primarily their size and location. FDG PET's utility in cancer imaging is its ability to differentiate some abnormalities based on metabolic or molecular function. Detecting alteration in glucose metabolism within cells is unique to PET technology.

An FDG PET scan can be interpreted based on qualitative and/or semi-quantitative evaluation. Qualitative FDG PET involves making assessments by visually interpreting the scan results. Metabolically active areas of the body "light up" on an FDG PET scan more so than less active areas. Metabolically active areas may include areas of cancer, inflammation, and benign cellular activity. Semi-quantitative evaluation uses the glucose metabolic rate of a tumor and, through computer software, determines a numeric value representing the metabolic activity for that tumor. Tumor-to-background ratio is a semi-quantitative method that compares a tumor's glucose uptake to the glucose uptake of surrounding or background tissue. This ratio is reported as standardized uptake value (SUV) and takes into account such factors as patient weight and injected FDG dosage, as well as the time lapsed from injection to metabolic imaging. FDG PET has been proposed as one possible test for determining the diagnosis, initial staging, restaging, and monitoring response to therapy for many cancers.

On February 24, 2003, CMS began an NCD process for FDG PET for brain, cervical, ovarian, pancreatic, small cell lung, and testicular cancers. This is a continuation of numerous NCDs in the past on many disparate types of cancer. Unfortunately, there is a paucity of published, methodologically robust, peer-reviewed clinical research data to support most of these requests. In some instances in the past, we have determined that enough evidence existed to warrant some limited coverage for some of these cancers. However, most of the recent NCD requests lacked sufficient evidence to determine a benefit and therefore remained noncovered. In addition, there is a high likelihood that opening NCDs for additional cancers, based on our conversations with the National Cancer Institute's Biomedical Imaging Program, would lead to the same outcome.

**III. History of Medicare Coverage**

CMS previously reviewed scientific literature and established coverage for many uses of FDG PET. A summary of each prior PET NCD follows. For each indication, there are specific coverage limitations listed in the CMS NCD Manual, Section 220.6.[1] A synopsis of the CMS NCD Manual Section 220.6 appears as Appendix D.

In addition to these positive coverage determinations, there have been many noncoverage determinations, some based upon evidence of lack of benefit and some based upon lack of evidence. Those are summarized in Appendix C.

For services performed on or after March 14, 1995, CMS covered PET using Rubidium 82 (not FDG) as the tracer for noninvasive imaging of myocardial perfusion in patients with known or suspected coronary artery disease.

Beginning January 1, 1998, FDG PET was covered when used for the initial staging of suspected metastatic non-small cell lung cancer (NSCLC) and for the characterization of suspected solitary pulmonary nodule (SPN).

On July 1, 1999, FDG PET coverage was expanded to include 3 additional oncology indications. These were: 1) location of recurrent colorectal tumors when rising CEA suggests recurrence; 2) staging and restaging of lymphoma only when used as an alternative to gallium scan; and 3) evaluating recurrence of melanoma prior to surgery only when used as an alternative to gallium scan.

On July 10, 2000, CMS received a request for broad coverage of FDG PET for 22 oncologic, cardiac, and neurologic conditions.[2] Included in the request was coverage of FDG PET for brain, cervical, ovarian, pancreatic, small cell lung, and testicular cancers-the same cancers comprising this current request. CMS commissioned a technology assessment (TA) from the AHRQ and referred the issue to the Medicare Coverage Advisory Committee (MCAC) for consideration. In a decision memorandum of December 15, 2000, based on available evidence, CMS announced its intent to expand coverage of FDG PET to include the indications listed below in Table 1. At that time, CMS did not find sufficient evidence to support coverage of FDG PET for the other indications included in the request, of which brain, cervical, ovarian, pancreatic, small cell lung, and testicular were a part. As a result, the December 15, 2000 decision memorandum announced a national non-coverage determination for these six cancers.

Table 1: Expanded coverage announced in decision memorandum of December 15, 2000

| Effective Date | Clinical Condition | Coverage |
|---|---|---|
| July 1, 2001 | Non small cell lung cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Esophageal cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Colorectal cancer | Diagnosis, staging, and restaging |
| July 1, 2001 | Lymphoma | Diagnosis, staging, and restaging |
| July 1, 2001 | Melanoma | Diagnosis, staging, and restaging. Non-covered for evaluating regional nodes. |
| July 1, 2001 | Head and neck (excluding central nervous system and thyroid) | Diagnosis, staging, and restaging |
| July 1, 2001 | Refractory seizures | Pre-surgical evaluation |
| July 1, 2001 to September 1, 2002 | Myocardial Viability | Following inconclusive SPECT |

On December 15, 2000, CMS accepted a request for FDG PET for diagnosis of early dementia in certain geriatric patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease. CMS commissioned a TA from AHRQ and presented the issue to the MCAC Diagnostic Imaging Panel for consideration. The MCAC Executive Committee then met and ratified the Panel's recommendations. In a decision memorandum of April 16, 2003, based on available evidence, CMS announced it would maintain noncoverage of FDG PET for the requested indications. On October 7, 2003, CMS accepted a request for reconsideration for a narrow use of FDG PET in the diagnosis of Alzheimer's Disease (AD). Effective on September 15, 2004, CMS expanded coverage specifically for patients with early dementia for whom the differential diagnosis between frontotemporal dementia and AD remained uncertain after a comprehensive clinical evaluation. In addition, coverage was expanded for use of FDG PET in the diagnosis and treatment of other patient groups with early dementia or those with mild cognitive impairment (MCI) in the context of protocol-driven, controlled clinical investigations that evaluate the effect of FDG PET use on clinical outcomes and meet other stipulated criteria.

On October 18, 2001, CMS accepted a request for FDG PET for diagnosing, staging, restaging, and monitoring therapy for soft tissue sarcoma. CMS commissioned a TA from AHRQ to evaluate the available literature. CMS determined that the evidence was not adequate to conclude that FDG PET was reasonable and necessary for the requested indications. As a result, a decision memorandum of April 16, 2003 announced CMS would maintain noncoverage of FDG PET for soft tissue sarcoma.

Beginning in July 2001, CMS allowed only specific types of PET systems to be covered according to their design characteristics. These characteristics included so-called full-ring, partial-ring, and coincidence systems.[3]

For services performed on or after October 1, 2002, FDG PET coverage was expanded to include two additional applications. For breast cancer, FDG PET was covered for certain women as an adjunct to standard imaging for staging or restaging and as an adjunct to standard imaging for monitoring response to therapy when a change in therapy is anticipated. For myocardial viability, FDG PET was covered for initial diagnosis or following inconclusive SPECT prior to a revascularization procedure.

For services performed on or after October 1, 2003, FDG PET coverage was expanded to include two additional applications involving two different radiopharmaceuticals. FDG PET was covered for restaging of recurrent or residual follicular cell thyroid cancer under certain conditions. PET using ammonia N-13 as the tracer was covered for noninvasive imaging of myocardial perfusion.

**IV. Timeline of Recent Activities**

| | |
|---|---|
| **February 24, 2003** | CMS accepted five formal NCA requests. Requests included brain, cervical, pancreatic, small cell lung, and testicular cancers. |

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| **March 24, 2003** | CMS accepted a formal NCA request for ovarian cancer. |
| **March 24, 2003** | CMS asked AHRQ to commission a TA of FDG PET for six cancer indications. |
| **February 12, 2004** | TA received. |
| **February 27, 2004** | Staff from CMS, the National Cancer Institute's Cancer Imaging Program, and AHRQ discussed FDG PET imaging for the specific oncologic indications in this decision memorandum. |
| **October 14, 2004** | CMS announced expanding this NCA to also address a potentially different process for determining when a PET scan is reasonably and necessary for all cancers that are currently noncovered. We welcomed public comment suggesting how CMS might do this. |

**V. Food and Drug Administration (FDA) Status**

The FDA approval letter for new drug application NDA 20-306, dated June 2, 2000 included the following language:

"This new drug application provides for the use of Fluorodeoxyglucose F-18 injection for the following indications:

Assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.... We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter..."[4]

The FDA has cleared PET devices, along with various software packages used to perform PET for general diagnostic use, through the 510(k) clearance process.

**VI. General Methodological Principles of Study Design**

When making national coverage determinations under §1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. A detailed account of the general methodological principles of study design agency staff utilizes to assess the relevant literature on the therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of diagnostic studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.[5]

**VII. Evidence**

**A. Introduction.**

Consistent findings across studies of net health outcomes associated with an intervention or diagnostic test as well as the magnitude of its risks and benefits are key to the coverage determination process. For this decision memorandum, CMS commissioned an external TA from AHRQ to review the published clinical evidence on use of FDG PET in the following six cancers: brain, cervical, ovarian, pancreatic, small cell lung, pancreatic, and testicular. CMS staff reviewed the commissioned TA, evaluated the individual clinical studies included in that document, and searched for any additional relevant articles subsequently published for all six cancers to determine if use of FDG PET improved net health outcomes when compared with conventional imaging modalities such as CT or MRI. In addition to our review of the clinical and scientific literature, we sought information from professional societies and searched for evidence-based practice guidelines, other technology assessments, consensus statements, and position papers.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but include beneficial or adverse clinical effects, such as change in management due to test findings or, preferably, improved health outcomes for Medicare beneficiaries. Accuracy refers to the ability of the test to distinguish patients who have or do not have the target disorder when compared to a reference standard. Measures used to determine accuracy include sensitivity (probability of a positive test result in patients with the disease) and specificity (probability of a negative test in patients who do not have the disease).

In evaluating diagnostic tests based on a reference standard (such as histology or prolonged clinical follow up), higher sensitivity and specificity values for a test like FDG PET when compared to another diagnostic modality would be an outcome of interest. In the absence of direct evidence to show that the diagnostic test under review improves health outcome, evidence of improved sensitivity or specificity could still prove useful as an intermediate outcome and data point estimate in the construction of a decision or evidence model (indirect evidence).

We will evaluate additional evidence and data submitted in response to this proposed decision..

**B. Discussion of Evidence Reviewed to Date**

**1. Assessment questions**

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve net health outcomes for Medicare patients?" The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. Assessment questions are listed in Appendix E.

**2. External systematic reviews/technology assessments**

Systematic reviews are based on a comprehensive and unbiased search of published studies to answer a clearly defined and specific set of clinical questions such as those related to the effectiveness of FDG PET in oncology applications. A well-defined strategy or protocol (established before the results of the individual studies are known) guides this literature search. Thus, the process of identifying studies for potential inclusion and the sources for finding such articles is explicitly documented at the start of the review. Finally, systematic reviews provide a detailed assessment of the studies included.[6]

As mentioned above, CMS commissioned a TA from the AHRQ to assess the value of FDG PET for listed oncology applications.[7]

**AHRQ TA Report on Positron Emission Testing for Six Cancers (Brain, Cervical, Small Cell Lung, Ovarian, Pancreatic, and Testicular)[8]**

*Search strategy*

An OVID search of the MEDLINE® database was conducted on April 18, 2003. Filters and limitations were used, and inclusion and exclusion criteria developed to identify articles to be reviewed. The search used applicable MeSH headings and textwords and resulted in 1058 citations for download and screening. Review of the abstracts resulted in accepting 226 citations that met the criteria for full-text article retrieval.[9] Articles providing information regarding technical feasibility only were excluded from further review. The number of articles providing information beyond the level of technical feasibility and addressing the analytic questions posed by CMS was as follows: brain (13), cervical (13), ovarian (10), pancreatic (24), SCLC (6), and testicular (11).

*Results and appraisal*

For complete results and appraisal of the AHRQ TA for each cancer, see Appendix F.

Brain: The TA authors noted that, although the use of FDG PET "may be a valuable modality" in distinguishing tumor from radiation necrosis, this assessment is "tempered by the results of three studies in which PET had comparable operating characteristics to the more accessible radionuclide studies (SPET/SPECT)."

The TA notes that it is unclear to what degree to which FDG PET performance for patients with truly indeterminate biopsy results will resemble the reviewed studies.

Cervical: The TA authors found with respect to FDG PET compared to conventional imaging in detecting pre-treatment metastasis that "there is fair to good evidence that PET is more sensitive than CT or MRI for detection of retroperitoneal nodal metastasis in patients with newly diagnosed cervical cancer."

Data suggest that PET is more sensitive than conventional imaging and has the potential to improve the early diagnosis of recurrent cervical cancer. These data are limited by small sample sizes. In addition, it is unclear whether improved early diagnosis of extra-pelvic recurrent cervical cancer leads to improved patient outcomes except in the setting of patients who have not previously received radiation.

Ovarian: The TA authors were unable to identify studies providing evidence for the utility of FDG PET in the initial staging of ovarian cancer. The authors concluded that FDG PET as an adjunct to conventional imaging "is not expected to be useful in the routine surveillance of patients with a history of ovarian cancer". The TA authors noted that for patients with rising CA-125 titer and negative conventional imaging there is "fair evidence to support the use of FDG PET for the detection of recurrent ovarian cancer".

Pancreatic: All studies reviewed assessed FDG PET only as an adjunct to other imaging and diagnostic modalities. No studies assessed FDG PET as a stand-alone method of diagnosing, staging, or monitoring for residual disease in pancreatic malignancy.

The TA notes that when FDG PET is used as an adjunct to conventional imaging in diagnosing metastatic disease, studies generally demonstrate a trend toward greater sensitivity of FDG PET compared to use of conventional imaging alone. However, the lack of complete comparisons between FDG PET and other conventional imaging techniques, and the lack of information on the quality of the comparators makes it difficult to assess the strength of this finding. The TA finds that specificity of FDG PET for the detection of metastasis is somewhat lower than the comparators.

With respect to FDG PET providing useful data in subpopulations with likely metastatic disease, the TA authors found it was difficult to identify subgroups that might achieve a substantially greater benefit from FDG PET data.

Diabetes and abnormal glucose metabolism, both of which are increased in the population with pancreatic malignancy and chronic pancreatic disease, can affect FDG PET results (usually with false negatives), but are treated inconsistently from study to study.

Small Cell Lung Cancer (SCLC): The TA authors commented that inadequate information was present to comment on the comparative performance of FDG PET relative to conventional imaging in staging SCLC; that no conclusion could be made in evaluating FDG PET performance compared to conventional imaging in restaging SCLC post treatment; and that, with regard to occult SCLC in paraneoplastic syndrome, the one study cited suggests a role for FDG PET, but "one that remains to be confirmed using larger sample size as well as a comparator test."

Testicular: TA authors concluded that the literature suggests a possible role for FDG PET in staging testicular cancer, but that studies had significant limitations and that further research was needed to confirm this finding.

In distinguishing between tumor versus necrosis, the TA authors note that in four studies FDG PET shows low sensitivity. This is largely due to the inability of FDG PET to distinguish between teratoma and necrosis/fibrosis. The TA authors commented that the specificity of FDG PET is consistently higher than that of CT in this context, but with significant study limitations.

In detecting recurrence in patients with rising tumor markers and negative CT, the authors note that one study addressed this question. FDG PET was found to have a sensitivity of 71% and a specificity of 83% for the diagnosis of recurrent germ cell tumor in patients with rising tumor markets but normal CT, but the study had significant limitations.

The TA can be found at http://cms.hhs.gov/mcd/viewtrackingsheet.asp?id=85.

**3. Internal technology assessments**

*Search strategy*

CMS conducted an OVID search of the MEDLINE® database on January 20, 2004 for the period January 1, 2003 through January 20, 2004. CMS used the same filters, limitations, and inclusion and exclusion criteria as those in the AHRQ literature search. This systematic review was conducted to help assure the most current review of published studies. Analysis of the abstracts resulted in 37 citations that met the criteria for full-text article retrieval. Articles providing information on technical feasibility were excluded from further review.

This systematic review of citations for brain cancer resulted in a single citation that met the criteria for full-text article review.

Two articles provided information for use of FDG PET in cervical cancer beyond the level of technical feasibility but focused on the evaluation of a specific technique, dual-phase or delayed FDG PET, and were thus not included in this review.

For ovarian cancer, analysis of the abstracts resulted in a single citation that met the criteria for full-text article retrieval.

For pancreatic cancer, analysis of the abstracts resulted in 33 citations that met the criteria for full-text article retrieval. Articles providing information on technical feasibility were excluded from further review. Eleven additional articles were found pertaining to FDG PET use related to pancreatic cancer.

There were no additional articles found pertaining to SCLC or testicular cancer beyond the level of technical feasibility.

CMS conducted an additional OVID search of the MEDLINE® database on October 1, 2004 for the period February 1, 2004 through September 15, 2004. CMS again used the same filters, limitations, and inclusion and exclusion criteria as those in the AHRQ literature search conducted on April 18, 2003. This review was conducted in order to help assure that our analysis included the most current review of published, peer-reviewed literature. Analysis of the abstracts from this search yielded 11 citations beyond the level of technical feasibility that met criteria for full-text review. One article was identified for brain cancer, six for cervical, two for ovarian, two for small cell lung, and none for either pancreatic or testicular cancers. None of the articles contributed uniquely to the findings of the AHRQ TA.

*Review*

CMS has carefully reviewed evidence for each of the six cancers. In general, the evidentiary base suffers from insufficient information about patient characteristics, the comparative imaging studies used, and the lack of standardized criteria for evaluating FDG PET results. Finally, no guidelines were located from any specialty society supporting routine use of FDG PET for patients with any of the six cancers.

Brain: The requested indications for appraisal of FDG PET compared with conventional imaging were: guided lesion biopsy of recurrent low-grade brain tumors in patients with an indeterminate MRI; distinguishing high-grade from low-grade tumors; distinguishing tumor from radiation necrosis in recurrent brain lesions; and as an adjunct to biopsy in the initial grading when the initial biopsy result was indeterminate grade II/III glioma.

There were twelve articles providing information beyond the level of technical feasibility, and the quality of these studies was inadequate to issue a positive coverage decision. There were several limitations to the data:

- test characteristics varied widely and sample sizes were small, thereby making it difficult to determine the clinical utility of an FDG PET scan and to determine when an FDG PET scan was reasonable and necessary
- FDG PET has similar operating characteristics to readily available imaging technology, potentially offering no increased benefit from an FDG PET scan
- there is uncertainty in generalizing FDG PET results from patients with definitive grade biopsies (the only literature provided) to settings with indeterminate grade

Cervical: The requested indications for appraisal of FDG PET compared with conventional imaging were: detection of pre-treatment metastases in newly diagnosed cervical cancer and residual or recurrent cervical cancer following treatment.

There were thirteen articles providing information beyond the level of technical feasibility.

Eight studies addressed the detection of pre-treatment metastases in newly diagnosed cervical cancer compared with conventional imaging. There was no literature that directly evaluated the impact of substituting or adding FDG PET to conventional imaging on patient health outcomes. Studies only provided estimates of FDG PET specificity and sensitivity. Although there remains concern about small sample sizes and other potential sources of bias, estimates were acceptable to use in extrapolating the potential impact of FDG PET on changing management when used as an adjunct to pre-treatment staging.

The body of evidence reviewed suggested improved sensitivity for FDG PET compared to conventional imaging in detecting nodal metastases generally, and para-aortic nodal metastases specifically, in patients with newly diagnosed cervical cancer. However, trial design features that could have introduced selection and observer bias and large confidence intervals preclude a conclusion that FDG PET should substitute for conventional imaging modalities currently in use for extended pre-treatment staging.

In summary, our analysis of the evidence and simulations undertaken using sensitivity and specificity estimates from the literature suggest that the addition of FDG PET subsequent to a negative CT or MRI can improve clinical decision-making.

Six articles assessed the diagnostic capabilities of FDG PET in detecting residual or recurrent disease. CMS found that no routine imaging modality has been established for post-treatment follow-up in cervical cancer and that uncertainty exists about the ability of early detection of residual or recurrent lesions in asymptomatic patients to affect clinical outcomes. In addition, the quality of these studies on post-treatment surveillance raised questions not only about the effects on clinical management or health outcomes but also about the sensitivity and specificity values reported for FDG PET.

Limitations included:

- lack of blinding for the pathologists or reference standard readers
- the clinical applicability of FDG PET for monitoring and restaging because the studies reviewed did not present results by clinically relevant subgroups, although treatment options varied depending on the primary treatment received
- low specificity values increasing the risk of a false positive result, a substantial concern in this group of patients who have already undergone anticancer therapies and, if thought to have recurrence, might lead to unnecessary and potentially harmful subsequent interventions

Ovarian: The requested indications for appraisal of FDG PET as an adjunct to conventional imaging were: initial staging, routine surveillance for recurrence, monitoring the response to chemotherapy, or for enhancing the accuracy of CA 125 testing.

There were eleven articles providing information beyond the level of technical feasibility. Specific limitations were that studies using FDG PET to detect recurrence in subjects with elevated CA 125 levels and negative conventional imaging were conducted in populations where the data from CA 125 levels alone were sufficient to produce perfect diagnostic accuracy. Hence, FDG PET could not improve the diagnostic results. These populations are unlikely to be representative of the true performance of either CA 125 or FDG PET. Additionally, when using FDG PET as an adjunct to conventional imaging in monitoring response to chemotherapy, we were unable to identify evidence that demonstrated improved outcomes with the addition of FDG PET to the standard workup.

Pancreatic: The requested indications for appraisal of FDG PET compared with conventional imaging were: detecting malignancy, metastasis, residual or recurrent disease, and defining the subpopulation(s) of patients for which adjunctive FDG PET is superior. There were twenty-four articles providing information beyond the level of technical feasibility. There were several limitations to the studies:

- details about both patients' conditions and the tests they received were sparse making it difficult to determine when an FDG PET scan was reasonable and necessary
- no consistency in study protocols which would permit a determination as to the clinical utility of FDG PET for this malignancy

Finally, a problem unique to pancreatic cancer was its association with diabetes and a general failure to follow recommended procedures for control of blood glucose to assist in obtaining accurate FDG PET results.

The quality of the studies was such that we were unable to determine a benefit to the addition of FDG PET to patient management.

Small Cell Lung Cancer (SCLC): The requested indications for appraisal of FDG PET compared with conventional imaging were: initial staging, restaging, and diagnosing occult disease in paraneoplastic syndrome.

There were six articles providing information beyond the level of technical feasibility and the quality of these studies was inadequate to issue a positive coverage decision. Limitations included:

- absence of comparator tests
- small sample sizes
- conflicting results pertaining to test accuracy
- retrospective nature

The literature available is not robust enough to determine a benefit of FDG PET in the management of SCLC.

Testicular: The requested indications for appraisal of FDG PET compared with conventional imaging were: initial staging, evaluating recurrence or residual disease, and determining recurrence in patients with rising serum tumor markers and a normal CT.

There were eleven articles providing information beyond the level of technical feasibility. Studies had several limitations including:

- mixed patient populations (both by cancer type and stage)
- a lack of blinding
- studies with conflicting results
- FDG PET was not compared to the same conventional imaging modalities in all studies, if compared at all
- FDG PET false positive rate depends on the time interval post chemotherapy[10] and there is no standard for this time interval

Given the significant limitations with all studies, some authors question the utility of FDG PET in testicular cancer. Authors also note the advantages of FDG PET over CT for initial staging are not clearly defined.

There are several difficulties with using FDG PET for distinguishing recurrence and residual disease from benign masses. FDG PET was not useful in detecting tumor of less than 0.5cm or teratoma of any size secondary to a low proliferation rate and glucose metabolism. Furthermore, FDG PET cannot reliably distinguish between teratoma and necrosis. Since FDG PET cannot reliably distinguish between teratoma, cancer and necrosis, regardless of a positive FDG PET, you will still resect the testicular mass (or at least perform a retroperitoneal lymph node dissection post chemotherapy if serum tumor markers are not elevated) because the standard of care is to leave no mass (or suspected recurrence) unexamined for fear of malignant transformation or "growing teratoma syndrome."

Notwithstanding the reportedly high specificity of FDG PET for detecting residual tumor, authors note that false positive results secondary to FDG PET accumulating in tissue macrophages are a common problem, especially post chemotherapy or if the patient has an infection. Finally, no method by itself is accurate enough to predict viability of residual masses.

As stated above, because of these limitations and the inability of FDG PET to distinguish between teratoma, necrosis and tumor, we do not foresee a role for FDG PET in changing management for this clinical scenario.

For detailed results by article, see AHRQ TA evidence tables, Appendix G.

**4. Professional Society Position Statements**

An on-line search of national cancer and surgical society websites found no position statements or clinical practice guidelines that mention FDG PET as part of the management of patients with brain, cervical, SCLC, or ovarian cancer.

The National Comprehensive Cancer Network's (NCCN) "2003 Practice Guideline for Pancreatic Adenocarcinoma,"[11] does not mention FDG PET among the imaging tests useful in the diagnosis and staging of pancreatic malignancy. The current guideline for diagnosis and treatment of pancreatic ductal adenocarcinoma, issued by the American Gastroenterological Association[12] makes no reference to the use of FDG PET. The National Cancer Institute in its February 2001,[13] "Report of the Pancreatic Cancer Progress Review Group," does not mention FDG PET for use in pancreatic cancer.

FDG PET for staging patients with SCLC is not recommended outside of a clinical trial setting.[14]

**5. Public Comments**

CMS received no comments or letters of support regarding FDG PET for any of the 6 cancers during the 30-day public comment period.

**VIII. CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

The adequacy of evidence for FDG PET's diagnostic accuracy and clinical utility in cancer (and subsequent CMS coverage decisions) may be categorized in three ways:

- Coverage based on evidence of benefit (positive evidence),
- Non-coverage based on evidence of harm or no benefit (negative evidence), and
- Non-coverage based on lack of evidence sufficient to establish either benefit or harm.

This section presents the agency's evaluation of the evidence available and coverage determinations reached for each request. It summarizes our analysis and conclusions for the cancers reviewed and the category, as defined above, in which they fit.

For cervical cancer, CMS considers the evidence adequate to conclude that FDG PET improves net health outcomes in the detection of pre-treatment metastases in newly diagnosed cervical cancer subsequent to negative conventional imaging and is therefore, reasonable and necessary for this indication. We will therefore, issue a positive coverage determination.

For testicular cancer, we believe the evidence is adequate to conclude that FDG PET does not provide a benefit and is therefore not reasonable and necessary for initial staging or evaluating recurrence or residual disease for patients with testicular cancer. CMS will issue a non-coverage determination for these indications.

In our review of the other cancer indications, we found, in general, insufficient evidence to reach a conclusion that FDG PET improved net health outcomes or changed patient management. This is consistent with many of our previous PET decisions. However, a sufficient inference of benefit can be drawn to support limited coverage if certain safeguards for patients are provided. This inference is based on both the pathophysiological basis for FDG PET's usefulness in cancer described in the Background Section as well as the positive coverage in several cancers for which there is evidence of sufficient quality to warrant coverage. While this does not provide the usual level of evidence that we require to ensure patient protection and appropriate utilization, we believe that patient protection can be provided by requiring data collection on patients receiving FDG PET scans for indications in which there is not sufficient evidence to reach a conclusion. Prospective clinical studies could be designed that would offer safeguards for patients to ensure appropriate evaluation and use of FDG PET scan results. This would offer the potential clinical benefits of FDG PET to Medicare beneficiaries with cancer while ensuring that service is provided in the context of a data collection that assures individualized analysis and evaluation of test results and patient health status.

We believe this to be a unique instance where general knowledge of a technology is well accepted while specific applications are not necessarily well proven. This lends itself to this type of coverage. We do not expect to apply this principle except in rare instances.

Before coverage of FDG PET for cancer can be extended widely, CMS believes additional data will need to become available to provide assurance that the current overall paucity of robust clinical evidence will not continue to impede the Medicare NCD process and thus potentially delay the coverage of beneficial services or the protection of beneficiaries from exposure to harmful or useless services.

FDG PET will continue to be refined in coming years and it is important to have a means of assessing the quality of patient care over time to ensure that positive outcomes are maintained or improved. Data from prospective clinical studies can be an invaluable aid in ongoing assessment of the quality of care provided to patients.

Collection of data in prospective clinical studies is needed to provide access to the information necessary to support the advancement of this technology.

CMS considers acceptable any one of the following three types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (IDE); or
- A clinical trial consistent with the evidentiary requirements for National Coverage Analyses (See Appendix A) and meeting specific quality standards (see Appendix B); or

- An FDG PET registry that is designed to provide additional information on the diagnostic accuracy and clinical utility of FDG PET diagnosis, staging, restaging, and/or monitoring of one or more cancers. Qualifying registries must ensure that specific hypotheses are addressed, appropriate data elements are collected; hospitals and providers are appropriately credentialed to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and hospitals and providers who do not comply with the data collection requirements are removed from the registry.

A registry must include criteria that ensure that:

1. Specific hypotheses are addressed

2. Hospitals and providers are appropriately credentialed to provide the FDG PET scan and interpret the results.

3. Participating hospitals and providers report data on all enrolled patients undergoing FDG PET scans for cancer therapeutic or diagnostic indications.
4. 

   Hospitals and providers who do not comply with the data collection requirements are removed from the registry.

5. The data set includes elements with the following characteristics:

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- Baseline patient characteristics
- Scan type and characteristics
- Scan results
- Results of all other imaging studies
- Facility and provider characteristics
- Information on cancer type, grade, and stage
- Long-term patient outcomes and disease management changes
- Anti-cancer treatment received

Further refinement of registry design is expected to occur based on public comments and further discussion with clinicians, methodology experts, and stakeholders. Specific hypotheses should be predefined and based upon analyses of combined data from all previous FDG PET studies. CMS strongly recommends that the sponsors and principal investigators of FDG PET clinical trials engage an independent, reputable imaging research center to pool the entire databases from their respective trials and conduct analyses to identify patient selection, scanner related issues and other research questions to more clearly define the data elements for the registry.

CMS recognizes that there are methodological limitations to the type of data and information that can be derived from registries and other prospective studies that lack formal control groups. However, there is much that may be learned from well designed and complete registries of diagnostic imaging. It will be possible to evaluate patterns of use of PET imaging and other imaging modalities in the context of specific disease characteristics and treatment choices. The registry would also allow providers to do quality assurance with substantial longitudinal information about patients' test results, treatments, and outcomes. The specified quality criteria for eligible registries will ensure that these studies provide informative and useful prospective clinical data.

While the evidence supporting the use of FDG PET for a number of the individual cancers addressed here would not, by itself, be sufficient to merit coverage, there are several considerations that lead CMS to consider these uses to be reasonable and necessary. First, the diagnostic performance and clinical utility of PET has been clearly documented for a number of other malignancies. Second, there is a common underlying molecular mechanism by which FDG PET provides functional information about tumors, which applies to malignancies for which the utility of PET has been shown, as well as the additional uses addressed in this decision. We therefore believe that the use of this technology for additional malignancies would be reasonable and necessary in the context of further clinical investigations. Selective use of this technology by clinicians experienced in its application to other cancers, and guided by information available through these registries, may well provide clinical benefit to patients. We would not expect this same logic to apply to other diagnostic technologies for which there had not yet been rigorous traditional diagnostic trials that document sensitivity, specificity and clinical utility.

CMS will continue to review evidence on request to reconsider the classification of FDG PET for individual cancers. We are particularly interested in seeing evidence that would permit us to make a coverage or non-coverage decision, i.e. to move an FDG PET indication from coverage under a registry or clinical trial to coverage or non-coverage based on definitive evidence of benefit, no benefit, or harm. If adequate new evidence is available, the decision may be changed to either "coverage based on evidence of benefit" or "non-coverage based on evidence of harm or no benefit."

We strongly encourage oncology imaging communities to develop evidence-based clinical practice guidelines for the use of PET and other cancer imaging modalities in diagnosing, staging, restaging, and monitoring of cancer patients.

**IX. Proposed Conclusions**

CMS proposes the following draft policy and invites comments on this policy for 30 days following the posting of this memorandum.

CMS has proposed that there is sufficient evidence to conclude that an FDG PET scan for the detection of pre-treatment metastases in newly diagnosed cervical cancer subsequent to negative conventional imaging would be reasonable and necessary, and CMS proposes to issue a national coverage determination (NCD) for this indication.

CMS has proposed that the evidence is sufficient to conclude that an FDG PET scan for staging or detecting recurrent or residual disease in testicular cancer would not be reasonable and necessary, and CMS proposes to issue a national non-coverage determination for this indication.

For all other indications in this decision memorandum, CMS has proposed that the evidence is sufficient to conclude that an FDG PET scan would be reasonable and necessary only when the provider is participating in and patients are offered enrollment in one of the following three types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (IDE); or
- A clinical trial consistent with the evidentiary requirements for National Coverage Analyses (See Appendix A) and meeting specific quality standards (see Appendix B) ;or
- An FDG PET registry that is designed to provide additional information on the diagnostic accuracy and clinical utility of FDG PET diagnosis, staging, restaging, and/or monitoring of one or more cancers. Qualifying registries must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are appropriately credentialed to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and hospitals and providers who do not comply with the data collection requirements are removed from the registry.

All other previous positive national coverage determinations will remain in effect. (See Appendix C.)

All other previous national non-coverage determinations based on evidence of lack of benefit will remain in effect. (See Appendix C.)

For all other indications for which CMS currently has a noncoverage determination (see Appendix C), CMS has proposed that an FDG PET scan would be reasonable and necessary only when the provider is participating in and patients are offered enrollment in one of the three types of prospective clinical studies described above.

APPENDIX A: General Methodological Principles of Study Design

APPENDIX B: Standards of Qualifying Clinical Trials

APPENDIX C: Proposed PET Oncology Coverage Indications

APPENDIX D: NCD Manual Summary

APPENDIX E: Assessment Questions by Cancer

APPENDIX F: Results and Appraisal of AHRQ TA by Cancer

APPENDIX G: External TA: Evidence Tables for Six Cancers

APPENDIX H: References

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1 http://www.cms.hhs.gov/manuals/103_cov_determ/ncd103c1_Part4.pdf

2 The decision memorandum and technology assessment addressing the July 10, 2000 request can be found at http://cms.hhs.gov/mcd/viewtrackingsheet.asp?id=85.

3 http://www.cms.hhs.gov/manuals/103_cov_determ/ncd103c1_Part4.pdf

4 Letter from Patricia Love, FDA, to Downstate Clinical PET Center. June 2, 2000. This letter is available on the FDA web site through a link at http://www.fda.gov/cder/approval/index.htm.

5 Deeks J. Systematic reviews of evaluations of diagnostic and screening tests. In Egger M et al, editors. *Systematic reviews in healthcare.* BMJ. 2001.

6 Hulley et al. *Designing Clinical Research.* 2001.

7 The TA report can be found at http://cms.hhs.gov/mcd/viewtechassess.asp?id=92-

8 Technology Assessment submitted to AHRQ by the Duke Center for Clinical Health Policy Research and Evidence Practice Center, David B. Matchar, MD, Shalini L. Kulasingam, PhD, Laura Havrilesky, MD, et al., December 2003.

9 See the TA for a complete description of the inclusion and exclusion criteria and search strategy.

10 because FDG accumulates in inflammatory tissue post chemotherapy

11 NCCN Practice Guidelines in Oncology v.1.2003. Pancreatic Adenocarcinoma.

12 AGA guideline: Epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. May 1999.

13 National Cancer Institute. Pancreatic Cancer: An Agenda for Action. February 2001.

14 Simon GR, Wagner H. Small cell lung cancer. *Chest* 2003 Jan;123(1 Suppl):259S-71S.

Back to Top